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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,658	11/29/2001	James M. Coull	BP0002-US	5256

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Applied Biosystems
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EXAMINER	
SISSON, BRADLEY L	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/996,658	COULL ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2006 and 18 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 November 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Prosecution Reopened- Finality Withdrawn

1. In view of the Appeal Brief filed on 13 March 2006, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

2. To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

3. A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

Drawings

4. Color photographs and color drawings are not accepted unless a petition filed under 37 CFR 1.84(a)(2) is granted. Any such petition must be accompanied by the appropriate fee set forth in 37 CFR 1.17(h), three sets of color drawings or color photographs, as appropriate, and,

unless already present, an amendment to include the following language as the first paragraph of the brief description of the drawings section of the specification:

> The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

5. Color photographs will be accepted if the conditions for accepting color drawings and black and white photographs have been satisfied. See 37 CFR 1.84(b)(2).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining the presence of a microbe (bacteria) in a human sample, wherein said method is practiced in accordance with the method steps of clams 1, 2 (detectable molecular probe is nucleic acid), and 8 with the added limitation that one is determining the species of microbe in a purified state using a detectable label, does not reasonably provide enablement for any and all manner of "determining," for any life form under any condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Quantity of Experimentation Necessary

The level and quantity of experimentation required to practice the full scope of the invention is vast, on the order of many man-years of trial-and-error experimentation with little, if any, reasonable expectation of success.

As presently worded, the method of claim 1 fairly encompasses "determining the presence, absence, position or number of detectable any organism immobilized to the solid carrier." (Emphasis added.) It is noted with particularity that it is the organism, not isolated DNA from the organism that is being immobilized to a solid support by a "binding partner".

The method fairly encompasses a method of identifying any organism in any sample from any other organism.

In accordance with claim 12, "the molecular probe stains all organisms of a domain, kingdom, group, class, genus, species, taxon, subclass, subspecies, serotype or strain without regard to whether or not this represents the organism of interest and wherein the binding partner is specific for the domain, kingdom, group, class, genus, species, taxon, subclass, subspecies, serotype or strain that is the organism of interest."

The specification is silent as to how one is to stain one, much less an entire population of organisms, be it single or multicellular, be immobilized to a solid support using a "binding partner."

The Amount of Direction or Guidance Provided and the Presence of Absence of Working Examples

The specification has been found to provide one example, and that it is located at pages 35-36 of the disclosure. As set forth there in *Salmonella choleraesuis* and *Listeria monocytogenes* cells were fixed and evaluated by both hybridization and antibody binding. While two types of organisms were studied, only a single nucleic acid probe was used. As set forth at page 36 of the specification, the antibodies were as follows:

> Two types of coded beads were received from Luminex, one coated with Salmonella-specific antibody (OEM Concepts, Toms River, NJ; the "Salmonella beads") and one with Listeria-specific antibody (OEM Concepts, Toms River, NJ; the "Listeria beads").

The specification has not been found to disclose through real or prophetic examples any one or combination of "molecular probes" that allow for the selection of any organism, or combination of organisms of interest. While an applicant is not required to teach each and every possible embodiment encompassed by the claims, the specification still must provide a full, clear, and concise description of the genus encompassed by the claims so that one would be readily able to determine if a species fell within the claims' scope, and to also reasonably suggest that applicant had possession of the invention at the time of filing. In support of this position, attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; *In re Wahlforss et al.*, 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

***

> We are of the opinion that a genus containing such a large number of species cannot properly be identified by the mere recitation or reduction to practice of four or five of them. As was pointed out by the examiner, four species might be held to support a genus, if such genus is disclosed in clear language; but where those species must be relied on not only to illustrate the genus but to define what it is, the situation is otherwise.

A review of the use of the probe according to SEQ ID NO.: 1 finds that the results are at best inconclusive, and at worst, grossly incorrect where the sample comprises a human cells. If, for example, one were to use a human cellular sample (e.g., blood) that is suspected of comprising one or more organisms, and the disclosed PNA probe was used, the probe would be indicating the presence of a microorganism even if no organism was present as the probe is complementary to a nucleotide sequence found in man, as well as being found in microbes. Accordingly, the probe would hybridize to the human sequences with equal specificity, leading the researcher to conclude that some microorganism was present, when such is not the case. For convenience, the disclosure as it relates to SEQ ID NO. 1 is reproduced below.

PNA Oligomers Prepared:

Table 1

Probe ID	PNA Probe Sequence	Seq. Id. No.
Bac Uni	Flu-OO-CTG-CCT-CCC-GTA-GGA-NH_2	1

All PNA sequences are written from the amine (N-) terminus to the carboxyl (C-) terminus. Flu = 5(6)-carboxyfluorescein; O = 8-amino-3,6-dioxaoctanoic acid

The disclosure has been construed as asserting that the probe according to SEQ ID NO. 1 is universal for bacteria. However, the same nucleotide sequence is also common to human. See the attached search results of search of Registry File in STN. Accordingly, the probe is not specific across any kingdom, phylum, class, order, family, and genus, much less any taxon, subclass, subspecies, serotype or strain (limitations of claims 12-14).

The Nature of the Invention

The claimed invention encompasses a method that allows for "determining the presence, absence, position or number of detectable organisms immobilized to the solid carrier" (claim 1, lines 22-23).

As noted above, the method explicitly requires the immobilization of the organism or organisms of interest onto a solid carrier. The specification is silent as to how anything other than single cells are to be immobilized to a support. Indeed, when as here the method fairly encompasses the analysis of any organism that can be present in a sample from any other organism, the claim encompasses not only "determining" of bacteria in a serum sample, but also the analysis of any organism that may have a symbiotic relationship with another organism, be it plant or animal. The aspect of simply immobilizing all of the members of the test class to the solid support is most daunting, if not impossible. It is further noted that in accordance with claim 11, "the solid carrier is selected from the group consisting of: a particle, a bead, a microscope slide, a micro titre [*sic*] plate, a membrane and an array." The specification is silent as to how anything other than single cell organisms are immobilized to a bead through immuno-affinity. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****

> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
>
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

In accordance with claim 10, the "binding partner is to be selected from the group consisting of: a carbohydrate, a lectin, a peptide, a receptor, a charged polymer and a protein." The specification identifies only one nucleic acid probe and two antibodies. No other description of any other functional and useful binding partner is identified. The specification has not been found to provide an adequate written description of those carbohydrates, lectins, peptides, receptors, charged polymers and proteins that will allow for the (i) the immobilization of only the organism of interest or (ii) the immobilization of the organism of interest as well as one or more

organisms to be "distinguished" (claim 1, lines 15-20). Even if an adequate number[1] of the vast, and widely divergent compounds had been described, the specification has not set forth reproducible method steps whereby any or all of the classes of "binding partners" can be used before or after reacting the organism with the "molecular probe" (e.g., *in situ* hybridization).

As presented above, the claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors,

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[1] Attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.
>
> ***
>
> We are of the opinion that a genus containing such a large number of species cannot properly be identified by the mere recitation or reduction to practice of four or five of them. As was pointed out by the examiner, four species might be held to support a genus, if such genus is disclosed in clear language; but where those species must be relied on not only to illustrate the genus but to define what it is, the situation is otherwise.

> such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The State of the Prior Art & The Predictability or Unpredictability of the Art

Prior, as well as post-filing art teaches of numerous problems confronting those of ordinary skill in the art. These problems have not been addressed by the instant disclosure. Absent specific guidance as to how these issues are to be overcome, one of ordinary skill in the art would be forced to trial-and-error experimentation in an effort to overcome these known issues.

Zhang et al., *Bioinformatics*, Vol. 19, No. 1, 2003, page 14, states:

> It is widely recognized that the hybridization process is prone to errors and that the future of DNA sequencing by hybridization is predicated on the ability to successfully cope with such errors. However, the occurrence of hybridization errors results in the computational difficulty of the reconstruction of DNA sequencing by hybridization. The reconstruction problem of DNA sequencing by hybridization with errors is a strongly NP-hard problem. So far the problem has not been solved well.

Chan (US Patent Application Publication US 2002/0119455 A1):

> [0018] In practice, Probe Up methods have been used to generate sequences of about 100 base pairs. Imperfect hybridization has led to difficulties in generating adequate sequence. Error in hybridization is amplified many times. A 1% error rate reduces the maximum length that can be sequenced by at least 10%. Thus if 1% of 65,536 oligonucleotides gave false positive hybridization signals when hybridizing to a 200-mer DNA target, 75% of the scored "hybridizations" would be false (Bains, 1997). Sequence determination would be impossible in such an instance. The conclusion is that hybridization must be extremely effective in order to generate reasonable data. Furthermore, sequencing by hybridization also encounters problems when there are repeats in sequences that are one base less than the length of the probe. When such sequences are present, multiple possible sequences are compatible with the hybridization data. (Emphasis added.)

As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

- The purity of the nucleic acid preparation.
- Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.
- Length of homologous base sequences- any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.
- Ionic strength- the rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.
- Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.
- Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.
- Denaturing reagents- the presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.
- Incubation- the longer the incubation time, the more complete will be the hybridization.

- Volume exclusion agents- the presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.
- Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

The specification is silent as to how each of the art-recognized features is to be modified not only to allow for the accurate and reproducible hybridization between organism(s) of interest molecular probe, but to also allow for the accurate and reproducible formation of a second binding structure- that which forms between said organism(s) and a "binding partner," which, as set forth in claim 10, any of " a carbohydrate, a lectin, a peptide, a. receptor, a charged polymer and a protein." Clearly, the ionic strength of the hybridization buffer, and the presence of chaotropic agents could easily lead to modification of the charge of the "charged polymer" as well as modifications of the structure of molecules such as carbohydrates, proteins, peptides, and receptors. Absent basic starting materials and reaction conditions, one is forced to conduct trial-and-error experimentation. While an applicant is not required to disclose each and every possible embodiment, the specification still must enable the full scope of the invention, and to that end, essential starting materials and reaction conditions are required. *Genentech.*

Barany et al. (US 2007/0042419 A1), at paragraph 0036 teaches in part:

> For allele-specific oligonucleotide hybridization ("ASO"), the mutation must be known, hybridization and washing conditions must be known, cross-reactivity is difficult to

> prevent, closely-clustered sites due to interference of overlapping primers cannot undergo multiplex detection, and mutant DNA cannot be detected in less than 5% of background of normal DNA.

Choi et al. (US 2007/0042400 A1), at paragraph 0035, teach:

> [0035] In conventional methods of preparing nucleic acid, polysaccharides such as starch often co-precipitate with nucleic acid. When polysaccharides co-precipitate with nucleic acid, it is difficult to manipulate nucleic acids by amplification methods, such as PCR, or by other detection methods, such as hybridization detection. Polysaccharides may also inhibit digestion with restriction endonucleases and other enzymatic manipulations.

It is noted that the claimed method fairly encompasses the use of genomic DNA, and the use of an enzyme substrate as a label.

The method fairly encompasses determining the presence of an organism that is highly related, or very similar, to some other organism. Yasuno et al., (US 2007/0031829 A1), paragraph 0037, teach in part:

> Certain oligonucleotides hybridize to polynucleotides having complementary sequences. Although DNA hybridization is sequence-specific, it is difficult to completely exclude hybridizations towards very similar nucleotide sequences.

The specification is silent as to how one would be able to determine and identify hybridization between a probe and a target and the same probe and a "very similar nucleotide sequence." It is further noted that the claimed method does not require the use of any positive and/or negative controls.

Wang et al., (US 2007/0009954 A1), teach:

> [0004] A number of methods have been developed to score SNPs, including allele-specific hybridization, electrophoretic DNA sequencing, single-nucleotide extension using labeled chain terminators, the "Invader" assay (Third Wave Technologies, Madison Wis.), mass spectrometry, the 5' nuclease assay (Taqman; see below), etc. All of these

> methods entail assays that are either difficult or expensive to develop, or difficult or expensive to perform.

It is noted that the claimed method places no lower limit on the ability to accurately and reproducibly detect any binding between polymer and unit specific markers.

As evidenced above, the art is replete with known issues that directly impact the enablement of the claimed invention. A review of the instant disclosure fails to identify how these art-recognized issues are to be overcome such that the full scope of the invention can be practiced without the public having to resort to undue experimentation.

It is noted, for example, that the claimed method is to allow for "determining the presence, absence, position or number of detectable organisms immobilized to the solid carrier" (claim 1, lines 22-23). The method also requires the combination of technologies, that is, one is to employ a "molecular probe" (e.g., *in situ* hybridization) in one method step and to also apply a "binding partner" (e.g., immunoaffinity binding) in a different step, with the specificities of each being stipulated. The method places no lower limit on the detection level, and places no restriction on the types and combination of reagents used. Rowlen et al., (US 2006/0286570 A1) teach:

> [0004] A variety of methods exist for detection of molecular recognition events. Detection of molecular recognition events such as DNA hybridization, antibody-antigen interactions, and protein-protein interactions becomes increasingly difficult as the number of recognition events to be detected decreases.

The specification is silent as to how one is to make such determinations in an accurate and reproducible manner when "the number of recognition events to be detected decreases."

The claimed invention encompasses a method that allows for the selection of any one or combination of "organisms" that have, or lack, any feature of interest. As presently worded, the

feature of interest is without limit. All that is required is that the "organism [be] of interest" to the individual performing the assay/method. It matters not what causes the individual to have an interest in the organism. Indeed, the point of interest may be physiological, chemical, ancestral, behavioral, psychological, or some other aspect, or combination of characteristics/features.

As noted above, the method explicitly requires the immobilization of the organism or organisms of interest onto a solid carrier. The specification is silent as to how anything other than single cells are to be immobilized to a support. Indeed, the method fairly encompasses the analysis of multicellular organisms. The aspect of immobilizing all of the members of the test class to the solid support is most daunting, if not impossible.

It is further noted that in accordance with claim 11, "the solid carrier is selected from the group consisting of: a particle, a bead, a microscope slide, a micro titre [*sic*] plate, a membrane and an array." The specification is silent as to how anything other than single cell organisms are immobilized to a bead through immuno-affinity binding.

As presently worded, the claimed method fairly encompasses the practice of eugenics, which is contrary to the pubic order.

In accordance with claim 12, one is to use a "molecular probe [that] stains all organisms of a domain, kingdom, group, class, genus, species, taxon, subclass, subspecies, serotype or strain without regard to whether or not this represents the organism of interest and wherein the binding partner is specific for the domain, kingdom, group, class, genus, species, taxon, subclass, subspecies, serotype or strain that is the organism of interest." The teaching of but a single PNA probe (SEQ ID NO: 1) and two antibodies, each specific for a different species of

microorganism, does not reasonably suggest that applicant had possession of the invention as claimed, much less enable the full scope of the invention.

Response to argument

8. Argument is presented at page 10 of the Brief that "all of the limitations of the claimed subject matter are discussed in the specification with reference to the knowledge of the ordinary practitioner."

9. This argument has been fully considered and has not been found persuasive. Attention is directed to MPEP 2145.

> Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art.
> The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

10. Assuming *arguendo*, that claim limitations are "discussed," such is not to say that the claims are fully enabled. For reasons presented above, the claims are deemed to be non-enabled for those embodiments beyond the scope of that specifically identified above.

11. At page 10, bridging to page 13 of the Brief, argument is presented that the specification does provide an adequate written description of the molecular probes, citing definitions at pages 7 and 10 of the specification. Similar argument is also presented at page 15, last paragraph.

The above argument has not been found persuasive. As an initial matter, the issue is not whether the terms are definite as no rejection under 35 USC 112, second paragraph, has been made. Rather, the specification has not provided an adequate description of the essential starting materials and reaction conditions that would enable the full scope of the claimed invention. To provide a definition of what constitutes a nucleic acid or non-nucleic acid polymer is not the same as identifying an adequate and representative number of the full genus of "molecular probes" that would fully enable the scope of the claimed invention. As presented above, the specification has been found to disclose but one probe to be used in a hybridization reaction, and that is comprised of PNA, and is not specific for bacteria as asserted.

12. At pages 16-17 and 21 of the Brief argument is presented that the instant case is distinguishable from *Lilly* as "the present claims rely on the manipulation of known entities (e.g. nucleic acid probes, PNA probes and antibodies) that are often used by the ordinary practitioner to identify organisms at various taxonomic levels."

13. The above argument has been fully considered and has not been found persuasive as the claims are not limited to the use of only those "entities" that are "known." In short, applicant is arguing limitations not found in the claims. Further, the claims are not limited to the use of just those molecular probes identified (nucleic acid probes, PNA probes and antibodies). A review of the pending 50 claims finds that claims 1, 4, 7-18, 21, 22, 24-35, 38, 39, and 41-50 do not limit the term "molecular probe." A review of the specification finds the following definition at page 7, lines 29-30:

> As used herein, a "detectable molecular probe" is a probe or molecular probe that is detectable by instrument or method.

14. Accordingly, the claims have been construed as encompassing the use of any conceivable probe that "is detectably by [any] instrument or method," and not just the categories that appellant has asserted. Should appellant wish to limit the claims thusly, appellant is encouraged to consider inserting the limitations of claims 2 and 3 into claim 1, as well as similarly amend all other independent claims.

15. It is noted that applicant's representative at pages 11-13, 16, 18-19, 24, 25, and 27, offers publications as though they are expert testimony. The situation at hand is analogous to that of *Ex parte Gray* (BPAI, 1989) 10 USPQ2d 1922 where it was held that publications do not qualify as either evidence or expert testimony such as that provided in a declaration under 37 CFR 1.132. As set forth at 1928,

> The reason for requiring declaration or affidavit form is to obtain the assurances that any statements or representations made are correct, as provided by 35 U.S.C. 25 and 18 U.S.C. 1001.

The present showing does not provide such assurances.

16. Agreement is reached with appellant at page 27 of the Brief that an applicant is not required to expressly teach each and every conceivable probe sequence, target sequence and related organism. Indeed, the method of claims 1, 4, 7-18, 21, 22, 24-35, 38, 39, and 41-50 do not limit the term "molecular probe" or the target in the "organism" to where any nucleic acid binding takes place. Accordingly, the identification of an adequate number of probes such that they represent the genus of probes contemplated as well as the genus of targets to which they are

to bind, is needed. As shown above, the case at hand is analogous to that of *In re Shokal*, wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; *In re Wahlforss et al.*, 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary. (Emphasis added.)

In the instant case, the method fairly encompasses any and all manner of life forms. Using mammals as an example, it is noted that the class Mammalia encompass approximately 5,400 species (including humans), distributed in about 1,200 genera, 153 families, and 29 orders. The specification has not been found to disclosed even one example of a "molecular probe" (nucleic acid or otherwise) that can be used against any of these 5,400 species in performance of the claimed invention.

17. At page 28 of the Brief appellant asserts that the holding of non-enablement is a clear error, to which attention is directed to Example 1, the only example.

The above argument has not been found persuasive as the premise of the example is not disclosed. While applicant/appellant has demonstrated that they were able to achieve hybridization between a probe and isolated cultures of two forms of bacteria, the example does not show that any meaningful results are obtained when the sample is something other than pure cultures of microorganisms. If, for example, one were to use a human cellular sample (e.g.,

blood) that is suspected of comprising one or more organisms, and the disclosed PNA probe was used, the probe would be indicating the presence of a microorganism even if no organism was present as the probe is complementary to a nucleotide sequence found in man, as well as being found in microbes. Accordingly, the probe would hybridize to the human sequences with equal specificity, leading the researcher to conclude that some microorganism was present, when such is not the case. For convenience, the disclosure as it relates to SEQ ID NO. 1 is reproduced below.

PNA Oligomers Prepared:

Table 1

Probe ID	PNA Probe Sequence	Seq. Id. No.
Bac Uni	Flu-OO-CTG-CCT-CCC-GTA-GGA-NH_2	1

All PNA sequences are written from the amine (N-) terminus to the carboxyl (C-) terminus. Flu = 5(6)-carboxyfluorescein; O = 8-amino-3,6-dioxaoctanoic acid

18. The disclosure has been construed as asserting that the probe according to SEQ ID NO. 1 is universal for bacteria. However, the same nucleotide sequence is also common to human. See the attached search results of search of Registry File in STN. Accordingly, the probe is not specific across any kingdom, phylum, class, order, family, and genus, much less any taxon, subclass, subspecies, serotype or strain (limitations of claims 12-14).

19. Further, the specification, including Example 1, fails to address any of the art-recognized issues that would confront the ordinary artisan.

20. For the above reasons, and in the absence of convincing evidence to the contrary, claims 1-50 are rejected under 35 U.S.C. 112, first paragraph.

21. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

22. Claims 1, 4, 7-18, 21, 22, 24-35, 38, 39, and 41-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Said claims are deemed indefinite with respect to just what constitutes the metes and bounds of the expression "detectable molecular probe." A review of the disclosure finds a non-limiting definition at page 7, lines 29-30:

> As used herein, a "detectable molecular probe" is a probe or molecular probe that is detectable by instrument or method.

23. In the instant case, the target of the probe is not defined and as such, the metes and bounds of what constitutes the "probe" or "molecular probe" cannot also be readily determined.

24. It is further noted that in accordance with claims 1-6, 9-23, 26-40, and 43-50 the "detectable molecular probe" is not required to be labeled, yet is "detectable." Only claims 7, 8, 24, 25, 41, and 42 require the 'detectable molecular probe" be labeled. It is further noted that in accordance with claim 4, 6, 21, 23, 38 and 40 explicitly require that the probe not be labeled with a detectable moiety. Accordingly, it is less than clear how one has a detectable molecular probe when it does not comprise a detectable label.

25. Acknowledgement is made of claims 5, 22, and 39 requiring the use of an antibody that "specifically binds to a detectable molecular probe/target sequence complex." As an initial matter, there is no antecedent support for "target sequence." Rather, independent claims 1, 18, and 35 provide support for an "organism" of interest. Irrespective of the issue of adequate support and definition for "target sequence," there is no requirement that the antibody only bind to the "detectable molecular probe/target sequence complex." As presented in the specification, the antibody binds to an antigenic determinant located on the surface of the organism, not to the

detectable molecular probe, the target sequence, not to the complex of same. Applicant is urged to amend the claims such that there is support for the claim language and that the embodiment claimed more closely parallels the disclosed invention.

26. Claim 11 is indefinite with respect to certain members of the *Markush* group of identified solid carriers. As presently worded, the "solid carrier" can be a "particle" as well as a "bead" or "an array." A review of the specification fails to locate a definition that sets the metes and bounds of what constitutes "a particle." Further, the term "bead" is in reference to a shape of a carrier, and not an example or definition of just what the solid carrier is. Further, the term "array" is a description of the arrangement of some items, which do not require any solid carrier. The claim does not define what the "array" is comprised of, or what the solid carrier (upon which the array is fixed) is comprised of.

Claim Rejections - 35 USC § 103

27. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

28. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

29. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

30. Claims 1, 2, 4, 5, 7-19, 221, 22, 24-36, 38, 39, 41-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallner et al. (System. Appl. Microbiol. 19, 569-56 (1996)) in view of Fulton et al. (Clinical Chemistry, Vol. 43, No. 9, 1997, pp. 1749-1756), Stender et al. (Journal of Clinical Microbiology, Vol. 37, No. 9, September 1999, pp. 2760-2765), Nordentoft et al. (Journal of Clinical Microbiology, Vol. 35, No. 10, 10-1997, pp. 2642-2648), and US Patent 4,683,196 (McLaughlin).

31. Wallner et al., disclose a method where fluorescence *in situ* hybridization and immunofluorescence are combined for flow cytometric identification of bacteria. Wallner et al., (abstract) teach that the step of immunostaining steps can be performed either before or after the hybridization steps.

32. Wallner et al., page 570, left column, teach:

> The combination of these two highly specific molecular tools opens up the whole range of phylogenetic levels for the high resolution and automated identification of micro-organisms by flow cytometry.

33. The aspect of using a nucleic acid probe is considered to meet the limitation of applicant's "detectable molecular probe." Also, the aspect of using an antibody to bind the organisms is deemed to meet the limitation of applicant's "binding partner."

34. Wallner et al., has not been found to disclose using an antibody (binding partner) that is coupled to a solid carrier.

35. Fulton et al., disclose a method whereby fluorescent microspheres are used in a variety of binding assays. At page 1749, left column, Fulton et al., disclose that antigens, antibodies as well as oligonucleotides can be coupled to the fluorescent microspheres. Also disclosed in said column is explicit teaching that the assay system allows for both qualitative as well as quantitative immunoassays.

36. Fulton et al., page 1749, left column, teach that the system "provide[s] complete control of the flow cytometer and perform[s] real-time data processing, allowing [or] multiple independent reactions to be analyzed simultaneously."

37. Fulton et al., page 1749, right column, teach that up to 64 different reactions can be analyzed simultaneously.

38. Nordentoft et al., teach performing FISH. While Stender et al., performed their assay on bacterial cultures, Nordentoft et al., each conducting their FISH assay for *Salmonella* serovars on paraffin-embedded tissue sections.

39. Nordentoft et al., page 2643, left column, teach the nucleotide sequence of a "universal bacterial probe" as well as a *Salmonella* probe and nonsense probes.

40. As disclosed by Nordentoft et al., the nucleotide sequence of the universal bacterial probe is:

5'-G**<u>CTGCCTCCCGTAGGA</u>**GT-3'.

41. The highlighted and underlined nucleotides correspond 100% with the sole probe disclosed by applicant (SEQ ID NO. 1).

42. Nordentoft et al., page 2644, disclose a comparison of nucleotide sequences for numerous strains of *Salmonella*, as well as comparisons with five other genera of bacteria..

43. Neither Fulton et al., nor Nordentoft et al., teach production and use of binding partners (e.g., antibodies) that span classes of an organism of interest (e.g., bacteria).

44. McLaughlin teaches the production and use of antibodies that provide a means for the immunological detection of an entire class of microorganism in clinical samples.

45. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Wallner et al., by incorporating the use of fluorescent microspheres and detection system of Fulton et al., as such would have allowed the ordinary artisan to monitor 64 different assays at the same time. It would have also been obvious to said ordinary artisan to have incorporated the use of either genus-, species-, strain-, or serotype-specific probes as disclosed by Nordentoft et al., as such would have allowed the ordinary artisan to detect an organism of interest or to detect multiple organisms in a common assay, which when combined with Wallner et al., would "opens up the whole range of phylogenetic levels for the high resolution and automated identification of micro-organisms" (Wallner et al.). And it would have also been obvious to said ordinary artisan to have further modified the method of Wallner et al., by optionally including antibodies that allow for the immobilization/binding/capture of a class of microorganisms, as disclosed by McLaughlin.

46. Appellant, through their Brief, assert repeatedly that the aspect of detectable molecular probes as well as immobilized binding partner are well known in the art. As shown above, the aspect of combining both a nucleic acid hybridization assay with an immunoassay wherein the antibodies (binding partner) are immobilized on microspheres (a solid carrier) was also well known in the art. The nucleic acid probes as well as immobilized antibodies are all functioning in a predictable manner, and result in an expected end result. Attention is directed to the decision in *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

47. In view of the detailed teachings of the prior art, the ordinary artisan would have had a most reasonable expectation of success.

48. It is further noted that prior art is not limited to the four corners of the documentary prior art being applied. Prior art includes both the specialized understanding of one of ordinary skill in the art, and the common understanding of the layman. It includes "background knowledge possessed by a person having ordinary skill in the art. . . [A] court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR* at 1396.

49. Suggestion, teaching or motivation does not have to be explicit and "may be found in any number of sources, including common knowledge, the prior art as a while or the nature of the problem itself'" *Pfizer, Inc. v. Apotex, Inc.* 480 F.3d 1348, 82 USPQ2d 1321 (Fed. Cir. 2007) citing *Dystar Textilfarben GMBH v. C. H. Patrick Co.*, 464 F.3d 1356 (Fed. Cir. 2006).

50. For the above reasons, and in the absence of convincing evidence to the contrary, claims 1, 2, 4, 5, 7-19, 221, 22, 24-36, 38, 39, 41-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallner et al. (System. Appl. Microbiol. 19, 569-56 (1996)) in view of Fulton et al. (Clinical Chemistry, Vol. 43, No. 9, 1997, pp. 1749-1756), Nordentoft et al. (Journal of Clinical Microbiology, Vol. 35, No. 10, 10-1997, pp. 2642-2648), and US Patent 4,683,196 (McLaughlin).

51. Claims 3, 6, 20, 23, 37, and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wallner et al. (System. Appl. Microbiol. 19, 569-56 (1996)) in view of Fulton et al. (Clinical Chemistry, Vol. 43, No. 9, 1997, pp. 1749-1756), Nordentoft et al. (Journal of Clinical Microbiology, Vol. 35, No. 10, 10-1997, pp. 2642-2648), and US Patent 4,683,196 (McLaughlin) as applied to claims 1, 2, 4, 5, 7-19, 221, 22, 24-36, 38, 39, 41-50 above, and further in view of Stender et al. (Journal of Clinical Microbiology, Vol. 37, No. 9, September 1999, pp. 2760-2765).

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65. McLaughlin teaches the production and use of antibodies that provide a means for the immunological detection of an entire class of microorganism in clinical samples.

66. Neither Wallner et al., Fulton et al., Nordentoft et al., nor McLaughlin teach using PNA probes.

67. Stender et al., disclose a method of performing fluorescence *in situ* hybridization (FISH) using peptide nucleic acid probes so to differentiate between tuberculosis causing mycobacterium (MTC) and non-tuberculosis *Mycobacterium* (NTM) species in smears and *Mycobacterium* cultures.

68. Stender et al., page 2761, teaches method for making PNA probes.

69. Stender et al., page 2762, provides an alignment of *Mycobacterium* 16S rRNA sequences, clearly teaching areas of conserved nucleotide sequences as well as area of variability between numerous species.

70. Stender et al., page 2763, right column, teach that the MTC- and NTM-specific PNA probes used in their FISH assay "are well-suited for differentiation between MTC and NTM species…"

71. It would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Wallner et al., by incorporating the use of fluorescent microspheres and detection system of Fulton et al., as such would have allowed the ordinary artisan to monitor 64 different assays at the same time. It would have also been obvious to said ordinary artisan to have incorporated the use of either genus-, species-, strain-, or serotype-specific probes as disclosed by both Nordentoft et al., and Stender et al., and to have optionally included the use of PNA probes, as disclosed by Stender et al., as such would have allowed the ordinary artisan to detect an organism of interest or to detect multiple organisms in a common assay, which when combined with Wallner et al., would "opens up the whole range of phylogenetic levels for the high resolution and automated identification of micro-organisms" (Wallner et al.). And it would have also been obvious to said ordinary artisan to have further modified the method of Wallner et al., by optionally including antibodies that allow for the immobilization/binding/capture of a class of microorganisms, as disclosed by McLaughlin.

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Conclusion

77. Objections and/or rejections which appeared in the prior Office action and which have not been repeated hereinabove have been withdrawn.

78. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

79. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D., can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

80. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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